ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Enasidenib for Patients With Relapsed Acute Myeloid Leukemia and the *IDH2* Mutation

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H&O Which patients with AML are at higher risk for relapse?

CD Unfortunately, most adult patients with acute myeloid leukemia (AML) will relapse. Features associated with a higher risk of relapse include older age and higher-risk disease, based on genomic features, at diagnosis. High-risk genomic features include complex chromosome alterations or certain mutations, such as *TP53* or *FLT3*-ITD mutations. Patients with therapy-related AML also have a higher risk of relapse.

H&O How common are *IDH* mutations in patients with AML?

CD Isocitrate dehydrogenase (*IDH*) mutations in the *IDH1* and *IDH2* genes occur in approximately 20% of patients with AML. *IDH2* mutations are slightly more common than *IDH1* mutations, occurring in approximately 12% of patients with AML. These mutations occur more frequently in older patients. They are identified through molecular testing, typically as part of the initial bone marrow evaluation. They can also be identified in the peripheral blood if circulating leukemia cells are present. Patients who are newly diagnosed with AML should undergo routine molecular annotation for *IDH,* along with other mutations of clinical importance, including *FLT3*, *NPM1*, and *CEBPA*.

H&O What is the impact of the *IDH* mutation?

CD The presence of an *IDH1* or *IDH2* mutation promotes the development of leukemia by blocking normal differentiation or maturation of hematopoietic precursors (blasts) into normal white blood cells. The *IDH2* mutation is particularly important because there are now treatments that target it. Enasidenib (Idhifa, Celgene/Agios), previously known as AG-221, is a first-in-class, selective targeted mutant *IDH2* inhibitor. Enasidenib removes the differentiation block that leads to abnormal maturation.

> A clear benefit is that approximately 40% of patients with relapsed AML and an *IDH2* mutation benefit from enasidenib and experience an overall response.

H&O Could you describe your research into enasidenib?

CD The presence of an *IDH2* mutation leads to the production of an "oncometabolite" known as 2HG. 2HG can be measured in the blood of patients with *IDH* mutations. I examined previously collected blood samples of patients who were treated in a multicenter clinical trial of the Eastern Cooperative Oncology Group (ECOG)

to see if measurement of 2HG could predict patients who had *IDH* mutations at diagnosis, and also whether the detection of 2HG at the time of remission could indicate a higher risk of relapse. We found that pretreatment levels of 2HG strongly predicted for the presence of an *IDH1* or *IDH2* mutation, and that patients with *IDH* mutations who were treated with intensive chemotherapy and showed an ongoing presence of 2HG at complete remission had shorter overall survival. This original research led to my involvement in the early development of the targeted IDH inhibitors. I have been fortunate to treat many patients in the original clinical trial that led the US Food and Drug Administration (FDA) to approve single-agent enasidenib for relapsed/refractory AML in August 2017.

H&O What did this trial show?

CD This large, multicenter, international phase 1 study treated 239 patients. Results were recently published in *Blood*. The study identified 100 mg/day orally as the recommended dose. The impressive outcomes included an overall response rate of 40% and a complete remission rate of 20% in patients with relapsed/refractory AML. The median overall survival was more than 9 months. Among patients with a complete remission, the median overall survival was almost 2 years, which was very encouraging.

An important finding from the pivotal clinical trial is that the responses took time. The average time to response was 2 to 3 months, but reached up to 6 months. I encourage patients with stable disease to remain on enasidenib therapy for 6 months to see if they respond. This longer time to response is standard when treating patients with leukemia with other noncytotoxic therapies, including the hypomethylating agents azacitidine (Vidaza, Celgene) and decitabine (Dacogen, Otsuka).

H&O What is the toxicity profile of enasidenib?

CD There are 2 toxicities of special interest that should be mentioned: indirect hyperbilirubinemia and differentiation syndrome. Indirect hyperbilirubinemia refers to elevation of the total bilirubin, but not the direct bilirubin. The increase is not coming from the liver; it is related to off-target effects involving the UGT1A1 metabolism pathway. Indirect hyperbilirubinemia is typically not clinically significant.

Differentiation syndrome may also occur. Because enasidenib is a differentiating agent that releases the differentiation block of the *IDH2* mutation, some patients may develop rapid differentiation, which can lead to clinical signs and symptoms, such as pleural effusions, pericardial effusions, edema, weight gain, and leukocytosis. This constellation of symptoms is similar to that seen with all-trans retinoic acid (ATRA) differentiation syndrome. It responds quickly to corticosteroid therapy and hydroxyurea.

H&O What are the benefits and drawbacks to using enasidenib in patients with AML?

CD A clear benefit is that approximately 40% of patients with relapsed AML and an *IDH2* mutation benefit from enasidenib and experience an overall response. Also, enasidenib is well-tolerated. Unfortunately, among patients who do respond, most ultimately relapse. My hope is to see improved outcomes using enasidenib in newly diagnosed patients, and in combination with other effective therapies.

H&O Are there any ongoing studies of enasidenib?

CD There are 2 ongoing studies evaluating enasidenib in the frontline setting for patients with newly diagnosed AML. Study AG120-221-C-001 is combining enasidenib with standard intensive chemotherapy in the younger, fit population. Study AG-221-AML-005 is combining enasidenib with azacitidine in patients who are older and/or unfit, to see if the addition of enasidenib to standard therapy leads to more durable responses and improved survival.

A study of enasidenib for patients with myelodysplastic syndrome (MDS) and *IDH2* mutations recently opened at MD Anderson. The study will ultimately open to enroll patients from 6 different centers in the United States participating in the MDS Consortium. Approximately 5% to 10% of patients with MDS have an *IDH2* mutation. Patients with newly diagnosed, high-risk MDS will receive treatment with enasidenib and azacitidine. Patients who require treatment after standard frontline hypomethylating agents will receive enasidenib alone.

H&O Is enasidenib being studied in diseases other than AML and MDS?

CD The phase 1 trial enrolled a small cohort of patients with other hematologic malignancies, including MDS. These patient groups also had encouraging responses, which led to the ongoing clinical trial of enasidenib in MDS. *IDH2* mutations are less common among patients with solid tumors as compared with *IDH1* mutations, which occur frequently in patients with gliomas, carcinomas, and cholangiocarcinoma. However, a study of enasidenib for patients with various advanced solid tumors or

angioimmunoblastic T-cell lymphoma—another cancer with increased prevalence of *IDH2* mutations—was recently completed.

H&O Are there any other promising genetic targets in AML?

CD *IDH1* mutations occur in approximately 8% of patients with AML. The *IDH1* inhibitor ivosidenib (formerly known as AG-120) is in clinical trials, and results were updated at the 2017 American Society of Hematology meeting. Response and outcome measures appear similar to those seen with enasidenib.

Disclosure

Dr DiNardo is a member of the advisory boards and/or has served as an advisor to Agios, Celgene, Novartis, and Bayer.

Suggested Readings

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